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EXAMINER

OGUNBIYI, OLUWATOSIN A

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RESPONSE TO AMENDMENT

The amendment filed 3/16/09 has been entered into the record. Claims 1, 4, 6, 7, 9-16, 18-23, 49 and 61-82 are now pending and are under examination.

Objections/Rejections Withdrawn

1. The objection to claim 45 under 37 CFR 1.75 as being a substantial duplicate of claim 22 is withdrawn in view of the cancellation of the claim.

2. The objection to claim 7, 9-16, 20-23, 25-27, 30-36 and 44-54 for broadening the scope of claim 1 is withdrawn in view of the amendment to the claims.

3. The rejection of claims 18-23, 25-27, 30-36, 44-45, 54 and 58-60 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of the amendment to the claims.

4. The rejection of claims 1, 4, 6-7, 9-16, 25-27, 30-36 and 44-48 and 50-60 under 35 U.S.C. 112, first paragraph (scope of enablement) is withdrawn.

5. The rejection of claims 1, 4, 6-7, 9-16, 18-23, 25-27, 30-36 and 44-60 under 35 U.S.C. 112, second paragraph is withdrawn in view of the amendment to the claims.

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6 The rejection of claims 1, 46, 51, and 55 under 35 U.S.C. 102(b) as anticipated by Jones et al (Diseases of Aquatic Organisms vol. 33: 25-31, 1998) is withdrawn in view of the amendment to the claims.

Rejections Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7 The rejection of claims 18-23, 49 and newly added claims 64-78 rejected under 35 U.S.C. 112, first paragraph, because the specification while enabling for

1) an isolated *Piscirickettsia salmonis* 45 kDa protein comprising the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 4 and nucleic acids encoding said proteins and expression vectors and host cells comprising nucleic acids encoding SEQ ID NO: 2 or SEQ ID NO: 4;

2) an immunogenic composition comprising SEQ ID NO: 2 or SEQ ID NO: 4 and an immunogenic composition comprising an expression vector comprising the nucleic acid that encodes SEQ ID NO: 2 or SEQ ID NO: 4 and an immunogenic composition comprising a recombinant *Yersinia ruckeri* comprising an expression vector comprising the nucleic acid that encodes SEQ ID NO: 2 or SEQ ID NO: 4

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3) enabling for a method of protecting salmonid fish from salmonid rickettsial septicemia disease wherein the occurrence of infection by *P. salmonis* is delayed and reducing mortality due to *P. salmonis* infection, comprising administering an immunogenic composition as set forth above; does not reasonably provide enablement for “vaccines”.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The specification teaches that the p45 protein is obtained from the bacterium *Piscirickettsia salmonis* (see background p. 1-3 of the specification). The full length p45 antigen is SEQ ID NO: 2 with signal peptide and without signal peptide is SEQ ID NO: 4. The specification discusses other antigens obtained from other infectious agents infecting fish such as the VP2 and VP3 protein of the infectious pancreatic necrosis (IPN) virus. The specification teaches that a composition comprising a bacterin of *Yersinia ruckeri* carrying the full length nucleic acid encoding p45 antigen (SEQ ID NO: 2 with signal peptide) and oily adjuvant (Montanide ISA711) is administered to Atlantic salmon (see example 4 lines 11-24, example 7 p. 79-86). The specification teaches that relative percent survival (RPS) in vaccinated fish was 100% when the control mortality was greater than or equal to 60% whereas at the end of the trial RPS for the vaccinated group was 43.4% and that the results indicate that SRS was effective in reducing mortality from *P. salmonis* infection when fish were vaccinated by injection with 0.1 mL vaccine/fish. The specification teaches that said *Yersinia ruckeri* carrying the full length p45 antigen delayed the occurrence of infection by *P. salmonis* (p. 86 lines 4-10).

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The dictionary definition of vaccine is "A prophylactic or therapeutic material containing antigens derived from one or more pathogenic organisms which, on administration to man or animal, will stimulate active immunity and protect against infection with these or related organism (i.e. produce protective immunity) " (The Dictionary of Immunology, Herbert et al eds, Academic Press, 1995). As set forth above, the specification teaches that a composition comprising *Y. ruckeri* comprising nucleic acid encoding the full length p45 antigen with signal peptide and oily adjuvant was effective in reducing mortality and delaying infection from *P. salmonis* infection when fish were vaccinated by injection with 0.1 mL vaccine/fish.

The salmonid fish were still infected but the definition of "vaccine" requires protection from infection. The specification teaches that said *Yersinia ruckeri* carrying the full length p45 antigen delayed the occurrence of infection by *P. salmonis* (p. 86 lines 4-10). Thus, the specification provides for delaying of infection and reducing mortality but does not protect from infection as set forth in the definition of a vaccine and also does not correlate delaying of *P. salmonis* infection and reducing mortality with protecting any fish from salmonid rickettsial septicemia.

As set forth above, the specification is enabling for a method of protecting salmonid fish from salmonid rickettsial septicemia disease wherein the occurrence of infection by *P. salmonis* is delayed and reducing mortality due to *P. salmonis* infection, comprising administering an immunogenic composition comprising SEQ ID NO: 2 or SEQ ID NO: 4 or an immunogenic composition comprising expression vector that comprises the nucleic acid encoding SEQ ID NO: 2 or SEQ ID NO: 4 or an immunogenic composition comprising *Y. ruckeri* comprising an expression vector that comprises the nucleic acid encoding SEQ ID NO: 2 or SEQ ID NO: 4.

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Amendments to the instant claims to recite “immunogenic composition” instead of “vaccine” will obviate the instant rejection.

Applicants’ arguments and the response:

Applicants respectfully disagree. It is submitted, with respect, that the Examiner is taking an excessively narrow interpretation of his own dictionary definition. It is urged that the ordinary artisan, who has read the instant specification, and who has read the above-quoted dictionary definition, will appreciate that if the vaccinated fish benefit with, "delaying of infection and reducing mortality," as conceded by the Examiner, it is clear that the injected composition did in fact, "stimulate active immunity and protect against infection" as required by the dictionary definition. The Examiner is also asked to take administrative notice of the setting and conditions for the proposed vaccination. As explained by the Background section of the instant application, beginning at page 1, the intended recipients of the instant immunogenic composition are farmed fish. These are fish raised under crowded conditions, for a set duration of time before harvesting. Under these conditions, the fish are susceptible to economically significant infections. It is submitted that delaying of infection and reduced mortality will, it is urged, in fact protect the farmed fish population, individually and collectively, from the spread and progression of the pathogen(s). Under the circumstances, it is respectfully urged that no technically credible reason has been made of record that the inventive immunogenic composition(s) cannot be described, for convenience, as a vaccine, under the quoted dictionary definition. Further, it is well known that the patentee is his or her own lexicographer. The instant specification fully defines an inventive vaccine as including the above-discussed antigens throughout the specification.

Applicants’ arguments have been carefully considered but it is not persuasive. Applicant is correct in stating that the patentee is his or her own lexicographer. However, Applicants specification defines many terms in the "detailed description of the invention" section of the specification as filed but no definition of the term “vaccine” was found and thus the interpretation of the word “vaccine” as intended by Applicant cannot be construed absent a specific definition. An applicant is entitled to be his or her own lexicographer and may rebut the presumption that claim terms are to be given their ordinary and customary meaning *by clearly setting forth a definition of the term* that is different from its ordinary and customary meaning(s). See MPEP 2111.01.

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The definition of vaccine set forth above requires “protection from infection” i.e. that there is no infection. The instant specification teaches that a composition comprising a bacterin of *Yersinia ruckeri* carrying the full length nucleic acid encoding p45 antigen (SEQ ID NO: 2 with signal peptide) and oily adjuvant (Montanide ISA711) is administered to Atlantic salmon (see example 4 lines 11-24, example 7 p. 79-86). The specification teaches that relative percent survival (RPS) in vaccinated fish was 100% when the control mortality was greater than or equal to 60% whereas at the end of the trial RPS for the vaccinated group was 43.4% and that the results indicate that SRS was effective in reducing mortality from *P. salmonis* infection when fish were vaccinated by injection with 0.1 mL vaccine/fish. The specification teaches that said *Yersinia ruckeri* carrying the full length p45 antigen delayed the occurrence of infection by *P. salmonis* (p. 86 lines 4-10).

Therefore, according to the specification on p. 86 lines 4-10, the *P. salmonis* are not protected from infection but in fact are still infected as compared to control. The composition comprising said *Y. ruckeri* bacterin delayed infection and thus prolonged survival of the fish/reduced mortality. The vaccine definition teaches that vaccines are supposed to protect from infection, see definition of vaccine above. If the vaccine does not protect from infection, then a salmonid fish administered the instant composition (see for instance claim 73) will still be infected, develop disease and die. This is evidenced by the data in Applicants own specification stating that said *Y. ruckeri* bacterin delayed infection and reduced mortality.

The Office understands from the specification that the intended recipients of the instant immunogenic composition are farmed fish and understands the context of how the immunogenic composition is to be used. However, while the claims are read in light of the specification, it is

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important not to import into the claims limitations that are not part of the claim. See MPEP 2111.01. “Though understanding the claim language may be aided by explanations contained in the written description, it is important not to import into a claim limitations that are not part of the claim. For example, a particular embodiment appearing in the written description may not be read into a claim when the claim language is broader than the embodiment.” Superguide Corp. v. DirecTV Enterprises, Inc., 358 F.3d 870, 875, 69 USPQ2d 1865, 1868 (Fed. Cir. 2004).

Applicants do not define the term “vaccine” to mean “delaying of infection and reducing mortality”. Thus, “vaccine” is given its plain meaning which involves stimulation of active immunity and protecting against infection. Protecting from infection within the meaning of vaccine means that there is no infection and thus no disease and thus no mortality or death due to infection. See definition of infection which recites “invasion by and multiplication of pathogenic microorganisms in a bodily part or tissue, which may produce subsequent tissue injury and progress to overt disease through a variety of cellular or toxic mechanisms” (Definition of infection from American Heritage Dictionary of the English Language, 4th Edition, 2000). Thus, all it takes is a single pathogen to multiply and cause disease. Clearly, Applicants data indicate that the fish were still infected (delayed infection) and thus the end result was reduced death.

Amendments to the instant claims to recite “immunogenic composition” instead of “vaccine” will obviate the instant rejection and Applicants are enabled for a method of protecting salmonid fish from salmonid rickettsial septicemia disease wherein the occurrence of infection by *P. salmonis* is delayed and mortality due to *P. salmonis* infection is reduced by administering any of the immunogenic compositions set forth above.

New Objections/Rejections Based on Amendment

8. Claim 71-72 are objected to under 37 CFR 1.75 as being a substantial duplicate of claim 70. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Claims 70-72 are all drawn to the vaccine of claim 64 wherein the VP2 var protein is obtained from a transformed *Pichia pastoris* cell, BCCM Accession No. IHEM 20070 and the VP3 protein is obtained from a transformed *Pichia pastoris* cell, BCCM Accession No. IHEM 20072.

9. Claim 80 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 6. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Claim 80 is drawn to an isolated or recombinant nucleic acid encoding a ^{ps} p45 recombinant polypeptide consisting essentially of the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 4. Claim 6 is drawn to an isolated or recombinant nucleic acid encoding a ^{ps} p45 polypeptide comprising the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 4.

“Consisting essentially” in claim 80 is interpreted as “comprising”. Thus, claim 80 and claim 6 are substantial duplicates. The definition of “consisting essentially of” is set forth below and provides for “comprising” as used in claim 6.

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As used herein a polypeptide "consisting essentially of" or that "consists essentially of" a specified amino acid sequence is a polypeptide that (i) retains an important characteristic of the polypeptide comprising that amino acid sequence, e.g., the antigenicity of at least one epitope of the p45 protein, and (ii) further comprises the identical amino acid sequence, except it consists of plus or minus 10% (or a lower percentage), and preferably plus or minus 5% (or a lower percentage) of the amino acid residues. In a particular embodiment, additional amino acid residues included as part of the polypeptide are part of a linked Tag, such as a C-terminal His₆ Tag.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

10. Claims 1, 4, 6, 7, 9-16, 18-23, 49 and 61-82 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

The claimed invention is drawn to a product of nature. Products of nature are not patentable because they do not reflect the "hand of man" in the production of the product or manufacturing process. Diamond v. Chakrabarty, 206 USPQ 193 (1980). Additionally, purity of naturally occurring product does not necessarily impart patentability. Ex parte Siddiqui 156 USPQ 426 (1966). However when purity results in new utility, patentability is considered. Merck Co. V. Chase Chemical Co. 273 F. Supp 68 (1967). See also American Wood v. Fiber Disintegrating Co., 90 US 566 (1974); American Fruit Growers v. Brogdex Co. 283 US 1 (1931); Funk Brothers Seed Co. V. Kalo Inoculant Co. 33 US 127 (1948).

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In the instant case, the instant *P. salmonis* proteins or nucleic acids exists in nature and also natural processes provide for conservative amino acid substitutions or natural sequence variants. Furthermore, the recitation of "recombinant nucleic acid" in the claims does not provide for the "hand of man".

It is suggested that applicants amend the claims to recite "isolated" in order to obviate the rejection. It is noted that, for instance, claim 6 recites "isolated or recombinant nucleic acid". The amendment of such claims to recite "isolated nucleic acid" instead of "isolated or recombinant nucleic acid" will also obviate the instant rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

11. Claims 79-82 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a *P. salmonis* p45 recombinant polypeptide that consists essentially of at least 95% of the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 4; an isolated or recombinant nucleic acid encoding a *P. salmonis* p45 recombinant polypeptide consisting essentially of the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 4 and a *P.*

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salmonis recombinant polypeptide consisting essentially of the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 4 with at least one conservative amino acid substitution (claims 81-82).

It is noted that claim 82 does not specify an amino acid position for the particular substitutions listed 1-12.

The specification defines "consisting essentially" on p. 17 lines 16-25 as follows

As used herein a polypeptide "consisting essentially of" or that "consists essentially of" a specified amino acid sequence is a polypeptide that (i) retains an important characteristic of the polypeptide comprising that amino acid sequence, e.g., the antigenicity of at least one epitope of the p45 protein, and (ii) further comprises the identical amino acid sequence, except it consists of plus or minus 10% (or a lower percentage), and preferably plus or minus 5% (or a lower percentage) of the amino acid residues. In a particular embodiment, additional amino acid residues included as part of the polypeptide are part of a linked Tag, such as a C-terminal His₆ Tag.

The specification teaches that SEQ ID NO: 2 is the full length p45 protein and SEQ ID NO: 4 is the p45 protein without the signal sequence and from the teachings in the specification there is no amino acid variability in the amino acid sequence of SEQ ID NO: 4 and the portion of SEQ ID NO: 2 which does not have the signal sequence.

As to a *P. salmonis* 45 kDa protein (p45) or recombinant polypeptide comprising SEQ ID NO: 2 or SEQ ID NO: 4 comprising at least one conservative amino acid substitutions, this encompasses a genus of variants of said proteins comprising a range of different conservative amino acid substitutions i.e. conservative substitutions at 1 or 2 or 3 residues up to all residues of the full sequence being conservatively substituted. The conservative substitution(s) can occur

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anywhere in the proteins. Claims 81-82 further expands said genus because in addition to the at least one conservative substitution each member of said genus possesses variability in at least, for example, 5% plus or minus of conservatively substituted sequence based on the definition of "consisting essentially". This encompasses non-conservative amino acids substitutions, deletions and insertions. Claim 79 and 80 is drawn to a genus of variants of SEQ ID NO: 2 or SEQ ID NO: 4 comprising changes in up to 5% of the respective sequences. This covers substitutions, insertions and deletions in, for example, any 5% or less of the sequences. It is noted that claim 82 does not specify an amino acid position for the particular substitutions listed 1-12. Thus, indicated conservative substitutions can occur anywhere the amino acids to be substitute occurs. If all the substitutions take place, these will lead to a completely different protein having different chemical characteristics from the p45 antigen.

The definition of "consisting essentially" requires maintaining the antigenicity of at least one epitope of SEQ ID NO: 2 or SEQ ID NO: 4.

The specification does not describe the immunoepitopes of p45 protein (with or without signal peptide). The specification does not teach the protective immunoepitope(s) of a p45 protein or SEQ ID NO: 2 or SEQ ID NO: 4 so that one of skill in the art can envision which regions of the amino acid can be conservatively substituted and still retain immunogenicity and protectiveness. Further, the specification does not teach which 5% or 4% or 3% or 2% or 1% of the amino acid sequence of the members of said genus of conservatively substituted variants can be changed and still retain the ability to protect against infection. The specification does not teach which 5% or 4% or 3% or 2% or 1% of SEQ ID NO: 2 or SEQ ID NO: 4 can be changed and still retain the ability to protect against infection. The claims are drawn to a large number of

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variants having different possibilities of changes to the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 4. The specification does not teach an example or reduce to practice any variant of the instant proteins including those that comprise at least one conservative amino acid substitution that still protects from infection. The specification does not for example teach that protectiveness is retained when all the amino acid positions of the protein are conservatively substituted and does not teach any epitope of SEQ ID NO: 2 or 4.

Antibody epitopes are characterized by the art as either continuous or discontinuous (see pages 23-25, 27-33, Harlow et al., *Antibodies A Laboratory Manual*, Cold Spring Harbor Laboratory Press Inc., 1988). T cell epitopes are continuous peptide fragments of a polypeptide or antigen that have been processed by an accessory cell. The art recognizes that defining epitopes is not easy and there is a confusing divergence between the textbook definition of epitope and the definition that is in use in published descriptions of experimental investigations and that epitopes must be empirically determined (Greenspan et al., *Nature Biotechnology* 17:936-937, 1999). The specification clearly lacks description of any particular antibody epitope (i.e. antigenic determinant), either continuous or discontinuous that is within SEQ ID NO: 2 or SEQ ID NO: 4. Applicants clearly did not provide written description of any particular antibody-binding or T-cell binding epitope contained in the instant proteins and as such it is not clear which residue(s) can be altered and still be antigenic, consistent with the definition of "consisting essentially. Colman et al. (*Research in Immunology* 145: 33-36, 1994, p.33 column 2, p. 35 column 1) disclose that a single amino acid changes in an antigen can effectively abolish the interaction with an antibody entirely and that a very conservative amino acid substitution may abolish antibody binding and a non-conservative amino substitution may have little effect

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in antibody binding. This underlies the importance of the description of the immunoepitope (s) and which conservative amino acid substitutions or deletions or insertions or combinations thereof and where and how many changes can the immunoepitopes tolerate and still retain immunogenicity. Houghten et al. (New Approaches to Immunization, Vaccines 86, Cold Spring Harbor Laboratory, p. 21-25, 1986) taught the criticality of individual amino acid residues and their positions in peptide antigen-antibody interactions. Houghten et al state (see page 24):

"One could expect point mutations in the protein antigen to cause varying degrees of loss of protection, depending on the relative importance of the binding interaction of the altered residue.

A protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antigen that is precipitously or progressively unrecognizable by any of the antibodies in the polyclonal pool." Thus, making all the substitutions in claim 82 in the instant proteins above 400 amino acids long will most surely result in a different protein from p45 and will most surely result in destruction of the immunoepitopes of the p45 antigen. The specification does not reduce to practice such a protein.

Even though one could screen for which changes in SEQ ID NO: 2 or SEQ ID NO: 4 will maintain protection from infection, the courts have held that possession of a genus may not be shown by merely describing how to obtain members of the claimed genus or how to identify their common structural features. The written description requirement is separate and distinct from the enablement requirement (See also *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 920-23, 69 USPQ2d 1886, 1890-93 (Fed. Cir. 2004) and adequate written description requires more than a mere reference to a potential method for identifying candidate polypeptides. The purpose of the written description requirement is broader than to merely explain how to

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‘make and use’ [the invention] *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1560, 19 USPQ2d 1111, 1114 (Fed. Cir. 1991). The disclosure of only two members of the genus to which the claims are drawn full length p45 protein (SEQ ID NO: 2) and p45 protein without the signal peptide (SEQ ID NO: 4) is insufficient to describe the large and variant genus of proteins the scope of which is set forth above. In such an unpredictable art, as set forth supra, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus. See *Noelle v Lederman*, 355 F. 3d 1343, 1350, 69 USPQ2d 1508, 1514 (*Fed. Cir. 2004*) and *In re Alonso* (Fed. Cir. 2008-1079).

Since the specification does not describe the common structure i.e. epitope(s) possessed by said genus, the skilled artisan would not be able to readily envision which changes could be made to SEQ ID NO: 2 or SEQ ID NO: 4 that still maintain immunogenicity. Except for SEQ ID NO: 2 or SEQ ID NO: 4, the specification lacks written description for said variants SEQ NO: 2 or variants of SEQ ID NO: 4 that are immunogenic and maintain the antigenicity of at least one epitope of the p45 protein and Applicants as of the time of filing were not in possession of said variants.

12. Claims 79-82 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated *Piscirickettsia salmonis* 45 kDa protein comprising the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 4 and nucleic acids encoding said proteins and expression vectors and host cells comprising nucleic acids encoding SEQ ID NO: 2 or SEQ ID NO: 4, does not reasonably provide enablement for an isolated or recombinant nucleic acid encoding *P. salmonis* p45 recombinant protein consisting essentially of

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the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 4 (claim 80) and a *P. salmonis* recombinant polypeptide consisting essentially of the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 4 with at least one conservative amino acid substitution (claims 81-82).

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The facts that should be considered in determining whether a specification is enabling or if it would require an undue amount of experimentation to practice the invention include 1) the quantity of experimentation necessary to make or use the invention based on the content of the disclosure, (2) the amount of direction or guidance presented, 3) the presence or absence of working examples, 4) the nature of the invention, 5) the state of the prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breadth of the claims. *In re Wands*, 858 F.2d 731, 735 (Fed. Cir. 1988). The determination that “undue experimentation” would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404. While the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP § 2164.01(a) and the evidence as a whole, the factors that weigh more in making the instant enablement rejection are discussed below.

Nature of the Invention and the breadth of the claims

The breadth of the claim 81-82 encompasses variants of the instant sequences wherein one or several residues or all of the residues of SEQ ID NO: 2 or SEQ ID NO: 4 are conservatively substituted. It is noted that claim 82 does not specify an amino acid position for

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the particular substitutions listed 1-12. Thus, the substitutions can occur anywhere the amino acid to be replaced occurs. Thus, making all the substitutions in claim 82 in the instant proteins above 400 amino acids long will most surely result in a different protein from p45 and will most surely result in destruction of the immunoeptopes of the p45 antigen.

The disclosed use of the instant SEQ ID NO: 2 and SEQ ID NO: 4 comprising at least one conservative amino acid substitution and nucleic acids encoding such is for a vaccine to protect fish against *P. salmonis* infection (specification p. 3-4 under summary of the invention) or to make antibodies to be used in diagnostic kits or components in vaccines (p. 29 lines 22 to 29).

As to claims 79-80, the disclosed use of a p45 recombinant polypeptide consisting essentially of at least 95% of the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 4 and nucleic acid encoding a p45 recombinant protein consisting essentially of the amino acid sequence of SEQ ID NO: 2 or SEQ ID NO: 4 is for a vaccine to protect fish against *P. salmonis* infection (specification p. 3-4 under summary of the invention) or to make antibodies to be used in diagnostic kits or components in vaccines (p. 29 lines 22 to 29).

The specification defines “consisting essentially” on p. 17 lines 16-25 as follows

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As used herein a polypeptide "consisting essentially of" or that "consists essentially of" a specified amino acid sequence is a polypeptide that (i) retains an important characteristic of the polypeptide comprising that amino acid sequence, e.g., the antigenicity of at least one epitope of the p45 protein, and (ii) further comprises the identical amino acid sequence, except it consists of plus or minus 10% (or a lower percentage), and preferably plus or minus 5% (or a lower percentage) of the amino acid residues. In a particular embodiment, additional amino acid residues included as part of the polypeptide are part of a linked Tag, such as a C-terminal His₆ Tag.

Thus, the scope of claims 79-80 includes variants of SEQ ID NO: 2 or 4 that are still antigenic and variants (insertion or deletion variants) of the conservatively substituted mutants of the proteins of claims 81-82.

Amount of direction or guidance in the specification/presence or absence of working examples

The specification teaches that the p45 protein is obtained from the bacterium *Piscirickettsia salmonis* (see background p. 1-3 of the specification). The specification discusses other antigens obtained from other infectious agents infecting fish such as the VP2 and VP3 protein of the infectious pancreatic necrosis (IPN) virus. The specification teaches that a composition comprising a bacterin of *Yersinia ruckeri* carrying the full length nucleic acid encoding p45 antigen (SEQ ID NO: 2 with signal peptide) and oily adjuvant (Montanide ISA711) is administered to Atlantic salmon (see example 4 lines 11-24, example 7 p. 79-86). The specification teaches that relative percent survival (RPS) in vaccinated fish was 100% when the control mortality was greater than or equal to 60% whereas at the end of the trial RPS for the vaccinated group was 43.4% and that the results indicate that SRS was effective in reducing

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mortality from *P. salmonis* infection when fish were vaccinated by injection with 0.1 mL vaccine/fish. The specification teaches that said *Yersinia ruckeri* carrying the full length p45 antigen delayed the occurrence of infection by *P. salmonis* (p. 86 lines 4-10).

As to the issue of SEQ ID NO: 2 or SEQ ID NO: 4 comprising at least one conservative amino acid substitution, the specification however does not teach immunization with proteins consisting essentially of SEQ ID NO: 2 or 4 with at least conservative amino acid substitution or immunization or raising of antibodies to proteins that consist essentially of at least 95% of the amino acid sequence of SEQ ID NO: 2 or 4. The specification does not disclose the protective immunoepitopes of the p45 antigen full length (SEQ ID NO: 2) or without signal peptide (SEQ ID NO: 4). The specification does not correlate conservative acid substitutions in SEQ ID NO: 2 or SEQ ID NO: 4 or proteins that consist of at least any 95% of SEQ ID NO: 2 or SEQ ID NO: 4 with protection from salmonid rickettsial septicemia or reduction in mortality from challenge with *P. salmonis* or with production of antibodies specific for *P. salmonis*. The specification does not provide guidance as to whether the immunoprotective epitopes of SEQ ID NO: 2 or SEQ ID NO: 4 is maintained when the sequences comprise one or more conservative substitutions. For instance, conservative substitution of all positions of SEQ ID NO: 2 or SEQ ID NO: 4 results in a completely different protein sequence and the specification does not provide guidance as to whether this different protein can still protect against salmonid rickettsial septicemia (SRS) or reduction in mortality from challenge with *P. salmonis*. Similarly, the specification does not teach whether conservatively substituted variants of SEQ ID NO: 2 or SEQ ID NO: 4 which have least 95% identity to SEQ ID NO: 2 or SEQ ID NO: 4 (see claim 51 and dependent claims) protects from infection. The scope comprises conservatively substituted

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variants of SEQ ID NO: 2 or SEQ ID NO: 4 which further comprises other non-conservative substitutions (i.e. SEQ ID NO: 2 or 4 comprising multiple mutations). As set forth above, the specification also does not provide for uses (vaccines or making antibodies) of variants of the p45 antigen (conservatively substituted and/or 95% identical to SEQ ID NO: 2 and/or SEQ ID NO: 4).

Unpredictability/predictability in the art

Houghten et al (New Approaches to Immunization, Vaccines 86, Cold Spring Harbor Laboratory, p. 21-25, 1986) teaches the criticality of individual amino acid residues and their positions in peptide antigen-antibody interactions. Houghten et al state (see page 24): "One could expect point mutations in the protein antigen to cause varying degrees of loss of protection, depending on the relative importance of the binding interaction of the altered residue. A protein having multiple antigenic sites, multiple point mutations, or accumulated point mutations at key residues could create a new antigen that is precipitously or progressively unrecognizable by any of the antibodies in the polyclonal pool. Colman et al. (Research in Immunology 145: 33-36, 1994, p.33 column 2, p. 35 column 1) disclose that a single amino acid changes in an antigen can effectively abolish the interaction with an antibody entirely and that a very conservative amino acid substitution may abolish antibody binding and a non-conservative amino substitution may have little effect in antibody binding. Thus, guidance and/or working example is needed correlating one or more conservative amino acid substitutions and other non-conservative amino acid changes (deletions or insertions) in SEQ ID NO: 2 or SEQ ID NO: 4 with protection from *P. salmonis* or for production of antibodies that detect *P. salmonis*.

Quantity of Experimentation Necessary

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SEQ ID NO: 2 consists of 438 amino acid residues and SEQ ID NO: 4 consists of 411 residues. It would take a large amount of experimentation to screen each amino acid position or combination of amino acid positions of each protein to determine which conservative amino acid substitutions and/or which insertions or deletions maintains antigenicity same as that of the p45 antigen and therefore can make antibodies specific for *P. salmonis* and can be used to protect salmonid fish from *P. salmonis* infection.

It is noted that these issues were raised in the previous Office Action addressing claims to proteins comprising at least one conservative amino acid substitution and proteins that comprise at least 95% of the amino acid sequence (see claim 1, 54 and 55 in the claim set of 10/24/2008) and the rejected claims were amended or cancelled but the new claims present the same issue. In view of the above considerations, the specification is not enabling for the full scope of the claims.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 66, 69 and 78 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 66 recites the limitation "vaccine" in line 1. There is insufficient antecedent basis for this limitation in the claim because claim 61 from which claim 66, 69 and 78 depends does not recite "vaccine".

Status of Claims

Claims 1, 4, 6,7, 9-16, 18-23, 49 and 61-82 are rejected. No claims allowed.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Oluwatosin Ogunbiyi whose telephone number is 571-272-9939.

The examiner can generally be reached on M-F 8:30 am - 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Robert Mondesi can be reached at 571-272-0956.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

/Oluwatosin Ogunbiyi/
Examiner, Art Unit 1645

/David J Blanchard/
Primary Examiner, Art Unit 1643